PHOTOACOUSTIC IMAGING SYSTEM FOR FLUID FLOW VISUALIZATION AND BIOLOGICAL TISSUES CHARACTERIZATION

CHUA HUI LING

A thesis submitted in

fulfillment of the requirement for the award of the

Degree of Master of Electrical Engineering

Faculty of Electrical and Electronic Engineering

Universiti Tun Hussein Onn Malaysia

JULY 2020

To my beloved parents and supervisor, thank you.

ACKNOWLEDGEMENT

In full gratitude I would like to acknowledge the following individuals who encouraged, supported and assisted me in my journey.

Foremost, my deepest appreciation goes to my supervisor, Prof. Madya Dr. Audrey Huong for her unwavering guidance, enthusiastic encouragement and mentorship in all the time of research and writing of this thesis. She gave me freedom to explore and at the same time gave me the valuable advice whenever I faced problem. Her patience and support helped me overcome many problems and successfully finish this dissertation.

I would also like to acknowledge all the volunteers involved for their worthy support and cooperation throughout this research.

I extend my thanks to all my friends and everyone who have, directly or indirectly, helped me beyond their abilities. Finally, I would like to express my heartfelt gratitude to my parents and siblings for their encouragement, moral support and caring for me through so many hard times.

ABSTRACT

Photoacoustic (PA) imaging is a biomedical imaging modality, which work is based on the photoacoustic effect, to provide illumination of biological tissues with strong optical absorption contrast and high spatial resolution at a short scanning time. The drawbacks of some existing PA fluid imaging systems, which include expensive equipment and their maintenance cost, limited sensitivity in detecting signals from restricted regions. This research describes an in-house developed two-axis PA imaging system for investigation of fluid flow and photoacoustic signatures of biological tissues using a continuous laser beam of output wavelength 633 nm to deliver light to the targeted tissue samples and fluid. The resulting acoustic signal detected by a transducer was used to determine the amplitude of tissues optical absorption via the measured phase value (Φ). This research began with the validation of the functionality of the developed system using biological system comprised of a mock circulatory system overlaid by different parts of poultry namely fat, liver and muscle of different sizes. The validated system was then deployed for use on human subjects, and the considered experiment settings included at rest, under warm water and arterial blood flow occlusion conditions. This work reported a consistent increase in the PA signals of all tissues with both sample size and the fluid flow rate. In addition, fat tissues were found to produce the largest PA signals with mean ± standard deviation (SD) Φ = 1.12 ± 0.11, while muscle produced the least signals with Φ = 0.828 ± 0.20, which trend agreed well with the previous literature. It was found from the experiments on human subjects that phase difference ($\Delta\Phi$) was proportional to the change in the velocity of blood flow within microcirculation of an investigated site. The mean and SD of percent relative phase difference for these volunteers were calculated as 51.68 % ± 24.27 % and -68.57 % ± 14.78 % for warm water and blood flow occlusion condition, respectively. The overall sensitivity of the system is 77. 3%. This work concluded the feasibility of this system for non-invasive assessment and visualization of blood perfusion and biological tissues, which deemed it suitable for implementation in healthcare applications.

ABSTRAK

Pengimejan photoakustik (PA) ialah modaliti pengimejan perubatan yang berfungsi berdasarkan kesan photoakustik untuk memberikan pencahayaan kepada biologi tisu dengan kontras penyerapan optik yang kuat dan resolusi spatial yang tinggi dalam masa pengimbasan yang singkat. Kelemahan PA system yang sedia ada di pasaran, adalah mahal pada sistem dan kos membaikpulihnya, sensitivity terhad dalam mengesan signal di tempat yang terhad pada sampel. Kajian ini menerangkan sistem pengimejan PA dua paksi yang diciptakan untuk penyiasatan pengaliran cecair dan ciri-ciri photoakustik biologi tisu dengan menggunakan laser yang mempunyai pengeluaran gelombang 633 nm untuk menyampaikan pancaran cahaya kepada tisu dan cecair sampel yang disasarkan. Signal akustik yang dihasilkan dan dikesan oleh transduser digunakan untuk menentukan amplitud penyerapan optik oleh tisu melalui pengukuran nilai fasa (Φ). Penyelidikan ini telah bermula dengan mengesahkan fungsi sistem dengan menggunakan sistem biologi yang terdiri daripada bahagian sisa ternakan iaitu lemak, hati dan otot dengan saiz yang berbeza. Pengesahan penggunaan sistem kemudiannya digunakan pada subjek manusia, dan eksperimen yang dijalankan termasuk pada keadaan rehat, di bawah air suam dan pada keadaan oklusi di arus aliran darah. Kerja ini melaporkan bahawa mempunyai peningkatan yang konsisten dalam signal PA untuk semua tisu dengan kedua-dua saiz sampel dan kadar aliran bendalir yang berbeza. Di samping itu, tisu lemak telah didapati menghasilkan signal PA yang terbesar dengan min $\Phi = 1.12 \pm 0.11$, manakala otot telah menghasilkan signal yang paling rendah dengan min $\Phi = 0.828 \pm 0.20$, dan trendnya bersetuju dengan sastera sebelumnya. Telah didapati daripada eksperimen pada subjek manusia bahawa perbezaan fasa ($\Delta\Phi$) adalah berkadar dengan perubahan dalam had laju aliran darah. Perbezaan min dan standard perbezaan fasa relatif (%) bagi sukarelawan telah dikira sebagai $51.68\% \pm 24.27\%$ dan $-68.57\% \pm 14.78\%$ bagi keadaan panas dan oklusi aliran darah. Sensitif keseluruhan sistem ialah 77.3 %. Kesimpulannya, sistem ini sesuai untuk non- invasif dan visualisasi perfusi darah dan tisu biologi dan sesuai untuk dilaksanakan dalam aplikasi penjagaan kesihatan.

CONTENTS

TITLE			**i**
DECLARATION			**ii**
DEDICATION			**iii**
ACKNOWLEDGEMENT			**iv**
ABSTRACT			**v**
ABSTRAK			**vi**
CONTENTS			**vii**
LIST OF TABLES			**x**
LIST OF FIGURES			**xi**
LIST OF SYMBOLS AND ABBREVIATIONS			**xvi**
LIST OF APPENDICES			**xviii**
CHAPTER 1	**INTRODUCTION**		**1**
	1.1	Overview	1
	1.2	Research background	1
	1.3	Problem statement	5
	1.4	Objectives	6
	1.5	Scopes	7
	1.6	Research contribution	7
	1.7	Outline of thesis	8
CHAPTER 2	**LITERATURE REVIEW**		**9**
	2.1	Overview	9
	2.2	Current imaging techniques	10
	2.3	Photoacoustic (PA) imaging and its characteristics	11
	2.4	Different types of photoacoustic techniques	13

2.4.1 Photoacoustic spectroscopy 13
2.4.2 Photoacoustic endoscopy 15
2.4.3 Photoacoustic microscopy 16
2.4.4 Photoacoustic tomography 17
2.4.5 Evolution of PA imaging 18
2.5 Comparison of different types of PA imaging 20
2.6 Advanced photoacoustic imaging technologies 23
2.6.1 Vevo LAZR-X system 23
2.6.2 Modified ultrasound system (IU22) 25
2.6.3 EPOCH 650 26
2.7 Blood flow visualization and biological tissues characterization using PA imaging system 28
2.8 Factors affecting phase value of PA imaging 31
2.9 Image reconstruction 35
2.10 Summary 37

CHAPTER 3 METHODOLOGY 38

3.1 Overview 38
3.2 System description 39
3.3 Phantom microcirculatory and biological tissue system 41
3.4 Image reconstruction 44
3.5 Investigation of PA system performance 49
3.5.1 Poultry sample preparation 49
3.5.2 Transducer tissues separation 51
3.5.3 Underlaying fluid flow change 51
3.6 Analytical techniques 52
3.6.1 Fast-fourier transform (FFT) 52
3.6.2 Phase difference calculation 54
3.6.3 Sensitivity 54
3.7 Human subject microcirculatory perfusion investigation 55

CHAPTER 4	**RESULTS AND DISCUSSION**		**58**
	4.1	Overview	58
	4.2	System configuration	59
		4.2.1 Performance of fluid flow system	59
	4.3	Investigation of PA imaging system performance	61
		4.3.1 Phantom circulatory model	61
	4.4	Biological tissues characterization	67
		4.4.1 Size of poultry	67
		4.4.2 Optimal transducer-tissue separation	71
	4.5	Discussion on poultry characterization	74
	4.6	Image reconstruction	76
	4.7	Clinical investigation of microcirculation	80
	4.8	Sensitivity of system	84
	4.9	Summary	86
CHAPTER 5	**CONCLUSION**		**87**
	5.1	Overview	87
	5.2	Overall summary	87
	5.3	Recommendation for future work	89
	REFERENCES		**90**
	APPENDICES		**104**
	VITA		**114**

LIST OF TABLES

2.1	Comparison of PA imaging systems	20
2.2	A summary of technical specifications of PA systems	21
2.3	Comparison between advanced PA technologies	27
3.1	Technical specification of equipment	42
4.1	Calculated phase difference following changes in flow pressure (ΔP) induced by different voltage supplied to phantom circulation system	62
4.2	Tabulated phase value range for PA imaging of different poultry samples of varying size	70
4.3	Tabulated phase value range for PA imaging of different poultry sample transducer separation	73
4.4	Refractive index of chicken poultry [136]	74
4.5	Confusion table of fluid flow visualization	84
4.6	Confusion table on tissues characterization for different tissue size dimension	85
4.7	Confusion table of tissues characterization for different transducer-tissues separation	85

LIST OF FIGURES

1.1	An illustration of sequence of events in PA imaging (image drawn according to the description in Li *et al.* [6])	3
2.1	Light absorption spectra of melanosome, oxyhemoglobin and deoxyhemoglobin (data compiled by Kelly *et al.* [37])	11
2.2	Light penetration depth in tissues at different wavelength (data compiled by Ruggiero *et al.* [38])	12
2.3	Timeline evolution of PA imaging	19
2.4	Vevo LAZR system	23
2.5	Photoacoustic imaging of healthy (upper panel) and melanoma tumour bearing (lower panel) brains. *HbT* and StO_2 represent total hemoglobin concentration and oxygen saturation, respectively [74]	24
2.6	Modified Ultrasound System (IU22)	25
2.7	EPOCH 650	26
2.8	Mie scattering	31
2.9	Acoustic intensity measurement [107]	32
2.10	Field of view (FOV) according to the transducer type [108]	32
2.11	Propagation of light at the boundary of two different media	33
2.12	Delay and sum of signal [116]	35
2.13	The corresponding region of k-space [117]	36
3.1	Ultrafast modulated laser source. **A**: Laser source; **B**: RF driver; **C**: AOM; **D**: Function generator	39
3.2	Ultrasonic transducer system (prepared sample taken during experiment). **A**: PE tube, **B**: Transducer, **C**: Tissue, **D**: Water tank	40

3.3	2D positional stage	40
3.4	Water pump system	42
3.5	Schematic diagram of photoacoustic (PA) imaging system	43
3.6	ELLO 8 rotational motor for 2D imaging	44
3.7	The formation of 2D PA image via rotation motion of transducer	45
3.8	Flow chart of image reconstruction study	46
3.9	Flow chart of PA imaging system	48
3.10	Chicken fat sample size. **1**: 3 cm × 2 cm, **2**: 6 cm × 2 cm, **3**: 9 cm × 2 cm	50
3.11	Chicken liver sample size. **1**: 3 cm × 2 cm, **2**: 6 cm × 2 cm, **3**: 9 cm × 2 cm	50
3.12	Chicken muscle sample size. **1**: 3 cm × 2 cm, **2**: 6 cm × 2 cm, **3**: 9 cm × 2 cm	50
3.13	Experiment setup. Inset shows validation of measured system using V323-SU.	51
3.14	(Top) Time domain signal (Bottom) Calculated frequency domain signal from its time domain counterpart	53
3.15	Consort diagram of microcirculatory clinical trial	56
3.16	Image of investigated skin site taken during blood flow occlusion condition	57
4.1	Relationship between supplied voltage and calculated flow pressure	59
4.2	Relationship between the measured flow rate at the calculated flow pressure	60
4.3	Image of photoacoustic measurement using single transducer system	61
4.4	The measured time domain acoustic signal for different supplied	62
4.5	Linear regression model (solid line) for the relationship between measured phase value and flow pressure using PA system.	

	(from top to bottom: liver, muscle and fat)	65
4.6	Linear regression model (solid line) for the relationship between measured phase value and flow pressure using EPOCH system. (from top to bottom: liver, muscle and fat)	66
4.7	Phase value of different biological tissues according to the prepared size (measurement using PA system)	68
4.8	Phase value of different biological tissues according to the prepared size (measurement using EPOCH system)	68
4.9	The phase value of chicken poultry sample size of 9 cm × 2 cm with different transducer placement. Results measured from developed PA system.	71
4.10	The phase value of chicken poultry sample size of 9 cm × 2 cm with different transducer placement. Results measured from developed PA system.	71
4.11	Reconstructed image for fat sample using assemble PA system	76
4.12	Reconstructed image for liver sample using assemble PA system	77
4.13	Reconstructed image for muscle sample using assemble PA system	77
4.14	(Top) Location of scattering region during the experiment. (Bottom) Scattering effects on the reconstructed 2D images.	78
4.15	Effects of light absorption on the calculated phase value	79
4.16	Time domain acoustic signal for at rest condition	80
4.17	Time domain PA signal for at rest condition	81
4.18	Relative phase difference between acoustic and PA system at different condition	81

LIST OF SYMBOLS AND ABBREVIATIONS

A	-	Area
A_o	-	Attenuation
AI	-	Artificial Intelligent
AOM	-	Acousto-optic Modulator
AR-PAM	-	Acoustic Resolution
CIN	-	Contrast Induced Nephropathy
DAS	-	Delay and Sum
DC	-	Direct Current
FDA	-	Food and Drugs Administration
FFT	-	Fast Fourier Transform
FOV	-	Field of View
HbT	-	Hemoglobin concentration
HS	-	Harmonic Search
ICU	-	Intensive Care Unit
IVPA	-	Intravascular Photoacoustic
IVUP	-	Intravascular Ultrasonic Photoacoustic
LED	-	Light Emitting Diode
LCD	-	Liquid Crystal Display
LDF	-	Laser Doppler Flowmetry
MRI	-	Magnetic Resonance Imaging
NIR	-	Near-Infrared
NSF	-	Nephrogenic Systemic Fibrosis
OPO-PAT	-	Optical Parametric Oscillator Photoacoustic Tomography
OR-PAM	-	Optical Resolution
P	-	Pressure
ρ	-	Volume

PA	-	Photoacoustic
PAE	-	Photoacoustic Endoscopy
PAM	-	Photoacoustic Microscopy
PAS	-	Photoacoustic Spectroscopy
PAT	-	Photoacoustic Tomography
PE	-	Polyethylene
PET	-	Positron Emission Tomography
PLD-PAT	-	Pulsed Laser Diode Photoacoustic Tomography
PPG	-	Photoplethysmography
Q	-	Flow rate
RBC	-	Red Blood Cell
RF	-	Radio Frequency
SD	-	Standard Deviation
SMA	-	Sub-miniature version A
SMF	-	Single Mode Fiber
SNR	-	Signal-to-Noise
S_tO_2	-	Hemoglobin Oxygenation Levels
SO_2	-	Oxygen Saturation
US	-	Ultrasound Imaging
V	-	Voltage
V	-	Velocity
WM-DPAS	-	Wavelength Modulated Differential Photoacoustic Spectroscopy
1D	-	One Dimensional
2D	-	Two Dimensional
3D	-	Three Dimensional
Ψ_{re}	-	Real part signal
Ψ_{im}	-	Imaginary part signal
Φ	-	Phase value
$\Delta\Phi$	-	Phase difference
r_Θ	-	Rotational angle

LIST OF APPEDICES

APPENDIX	TITLE	PAGE
A	Inclusion criteria	104
B	Informed consent statement	108
C	Comparisons of reconstructed images	110
D	List of associated publications	112

CHAPTER 1

INTRODUCTION

1.1 Overview

This chapter is structured as follows: a research background of photoacoustic imaging is briefly explained in section 1.2. The problem statements of current technology and aims of study are discussed in section 1.3. The objectives of research works are listed in section 1.4 followed by scopes of study in section 1.5 and research contribution in section 1.6.

1.2 Research background

Biomedical imaging is a technique and process of generating visual representation of body parts for medical analysis. There are various types of biomedical imaging technologies available to guide treatment, as a prognosis tool and for non-invasive monitoring of diseases and therapy [1]. Imaging modalities such as Magnetic Resonance Imaging (MRI), X-ray computed tomography, ultrasound and spectroscopy are often used to diagnose diseases such as cancer in their early stage, which could then lead to more effective treatments. Photoacoustic (PA) imaging, or commonly known as optoacoustic or thermoacoustic imaging, is a biomedical imaging modality based on the photoacoustic effect. PA system, which is a hybrid method that combines optical and acoustic approach, was discovered in year 1880 by A. G. Bell through his photophone invention [2].

This technique promises a great potential to provide imaging and illumination of biological tissues with strong optical absorption contrast and high spatial resolution at a shorter scanning time of three seconds, which is close to real-time performance [3]. The common use of this technique includes its application in depth profiling of layered media, and for scanning tomography of scattering biological tissues using both focused and unfocused transducers. In PA imaging, non-ionizing laser (typically in the wavelengths of visible to near infrared light region) pulses are delivered into biological tissues. Some of the delivered energy would be absorbed and converted into heat, leading to transient thermoelastic expansion of around 5 ns to 10 ns, which shorter than thermal relaxation time [4, 5] and thus producing wideband (of MHz range) ultrasonic emission as shown in Figure 1.1 [6]. The This technology is termed as thermoacoustic imaging when radio frequency pulses are used [7].

The generated ultrasonic waves would be detected by an ultrasonic transducer before it was manipulated to produce images. It is known that optical absorption is closely associated with physiological properties, such as hemoglobin concentration and oxygen saturation [8]. As a result, the magnitude of ultrasonic emission, which PA signal is proportional to the local energy deposition, reveals physiologically-specific optical absorption contrast. In addition, the use of an *x*-*y*-*z* transitional stage in the system allows two dimensional (2D) or three dimensional (3D) images of the targeted areas to be formed [9]. In essence a PA image can be regarded as an ultrasound image, in which the contrast depends not only on the mechanical and elastic properties of the tissue, but also its optical properties, specifically optical absorption. As a consequence, it offers greater specificity than conventional ultrasound imaging with the ability to detect hemoglobin, lipids, water and other light-absorbing chromophores, and with greater penetration depth than purely optical imaging modalities that rely on ballistic photons [10]. In addition to the visualization of anatomical structures such as the microvasculature, this imaging technique is able to provide functional information such as blood oxygenation, blood flow and temperature [5, 11]. All of this can be achieved over a wide range of length scales from micrometres to centimetres with scalable spatial resolution. These attributes lead to the use of PA imaging to a wide variety of applications in clinical study [12], preclinical research and basic biology for studying cancer [13], cardiovascular disease [14], abnormalities of the microcirculation [15] and other conditions. This device was certified under CE 0086 to meet the provisions of the transposition of the Medical Device Directive

2007/47/EC within the country of origin of the Notified Body concerned with the device.

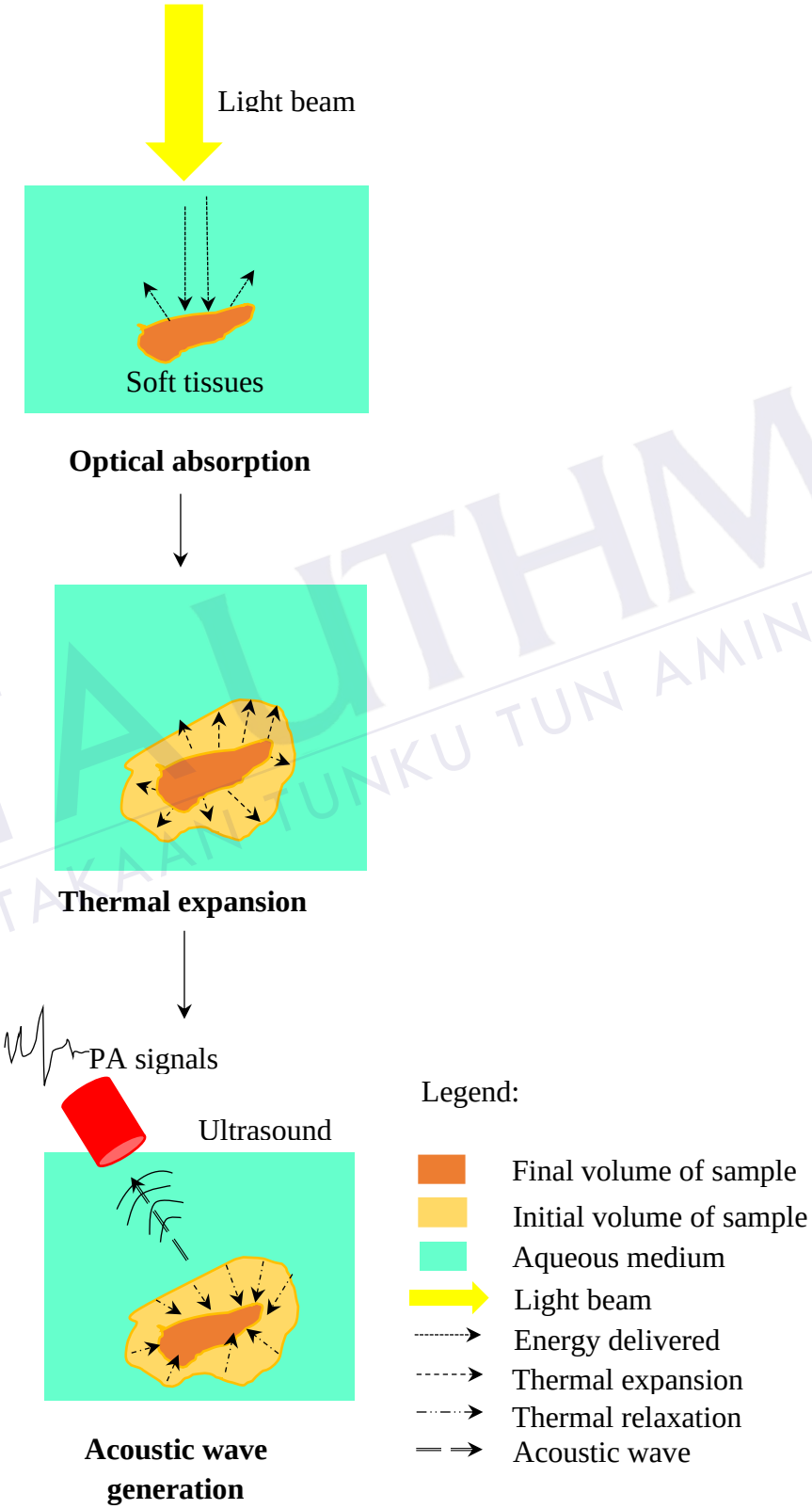

Figure 1.1: An illustration of sequence of events in PA imaging (image drawn according to the description in Li *et al.* [6])

Meanwhile Malaysia adopts the same health system as that of the British since its independence in year 1957, wherein the healthcare services are primarily provided to residents in urban area. Therefore in the Eleventh Malaysia Plan (11^{th} MP) the focus is on increasing accessibility and affordability of healthcare services for Malaysia population living in sub-urban and rural areas [16]. Strategies were designed to provide necessary environments and equipments required for effective delivery of healthcare services and activities. The Malaysian government accelerates efforts to provide quality healthcare services and increase capacity of facilities by targeting at underserved areas and focusing on mobile healthcare. Among the moves include launching of the first mobile clinic to provide basic screening and treatment for people in rural area in year 2010. Healthcare financing is a main challenge to provide equal healthcare services in Malaysia. Therefore the involvement of private sectors, especially those working closely with the ministry, is highly welcomed to provide healthcare services to community under the strict and constant monitoring of Ministry of Health (MOH). In addition the quality of healthcare has been improved; this includes rigorous standard on the use of radiation in medicine or diagnostic, such as the use of X-Ray is controlled by Atomic Energy Licensing Act 1984 (Act 304) to protect the patients from medical radiation overdoses [17]. It must also be mentioned that even though the use of contrast dye is necessary to enhance visualization, Food and Drugs Administration (FDA) warns on the use of exogenous dyes for imaging [8], wherein according to National Kidney Foundation, the retained dyes may cause Contrast Induced Nephropathy (CIN) and Nephrogenic Systemic Fibrosis (NSF). The latter are the diagnosis of the sudden decline of renal function after injection of contrast dyes, and there are no proven treatments for both CIN and NSF [18].

1.3 Problem statement

Despite government effort in socio-economic development plans, the inequality in services provided, especially for the rural population and hard-core poor [19], is still present. This is particularly in the medical imaging area, which technologies are important in diagnosis and treatment planning. Some functional imaging system such as MRI are limited to urban areas as this bulky machine is difficult to be delivered to rural areas. In addition to its expensive and time consuming operation, which would take around 15 to 90 minutes [20] to complete, this machine also involves complicated preparation procedure [21]. The X-ray imaging system is able to point out the fracture bone within body system, but it is not suitable for soft tissue imaging. The above mentioned imaging systems often required the use of exogenous dyes to enhance contrast during imaging. Meanwhile ultrasound (US) imaging is able to detect soft tissues condition at the price of poorer spatial resolution.

A photoacoustic image is related to the optical absorption in the tissue which corresponding to the incident photons of light source. It is an estimate of the distribution of acoustic waves that arise following the absorption of a pulse of light. The current market available PA devices that do not required the use of contrast agents include Modified Ultrasound System (IU22) and Vevo LAZR system. Both of the systems are, however, bulky and immobile. In addition, tunable dye laser commonly found in the design of PA system is expensive. The low-end systems would cost around RM 100,000 while high-end technology may be up to RM 1 million.

Coronary heart disease and cancer are reported as the main killer diseases in Asia [22, 23], therefore characterization of tissues would help in identifying the cause of certain diseases. While human biological traces are able to provide important evidence in a crime scene, messenger ribonucleic acid (mRNA) is used for identification of organ tissue types in forensic with the help of indicative markers [24, 25]. These techniques are, however, time consuming. It must be mentioned that [26] reported the use of PA spectrophotometer in forensic study to extract valuable information by analysis the signal from the investigated sample using model heat equation. However the main problem of PA approach is the fluctuation of filter used, which results in inaccurate result.

Previous reports [27, 28] showed Red blood cells (RBC) as the main parameter to investigate the blood flow and detection of atherosclerosis. Blood circulation is one

of the most important functions in body system since it supplies oxygen to the brain and other parts of organs. Even though ultrasound is normally used for the investigation, its drawback include poor imaging of gaseous organ [29].

There is room for improvement in the design of PA imaging. Photoacoustic system requires broadband detectors to capture the produced acoustic waves efficiently. Ideally, frequency and angle-dependent ultrasonic sensor should optimally be chosen for the measurements. In addition, some sensor arrays have limited elements [ref], which caused limited field of view for PA imaging. Therefore effective PA measurement of an investigation sample requires multiple sensors, which exerted demand on exhaustive calibration process to produce a single shared viewpoint.

Hence, an affordable low cost in-house assembled PA imaging system with short scanning time of less than 10 minutes using a suitable ultrasonic transducer for signals detection is necessary to ensure efficient and accurate measurement of result in fluid flow and tissues characterization.

1.4 Objectives

This research embarks on the following objectives:

i) To develop an affordable and near real time two-dimensional stage photoacoustic system for characterization of biological tissues and prediction of microcirculatory performance in both phantom and clinical studies.

ii) To investigate phase-resolved acoustic signature of different types of biological tissues and changes in this attribute with overlaying fluid flow rate.

iii) To validate the performance, specifically sensitivity, of the developed imaging system through the comparisons of the reconstructed image obtained from phantom and clinical studies with that given by EPOCH 650 and single point ultrasound system.

1.5 Scopes

To fulfill the stated objectives, the scopes of the project are:

i) A low cost laser source is used for illumination of both phantom and clinical samples while the 2D detection of photoacoustic signal is via ultrasonic transducer mounted on a fast response rotational stage (of maximum rotational speed of 430^{o}/second).

ii) Different parts of poultry samples namely liver, fat and muscle are used for investigation of different acoustic characteristics of tissues while different fluid velocity passing through the polyethylene tube (PE) tube is to mimic the different blood flow rate.

iii) The calculated photoacoustic signal phase value, Φ, is compared with that measured using EPOCH 650.

iv) The sensitivity of in-house assembled PA imaging system is calculated to evaluate its efficiency.

1.6 Research contribution

In this thesis, a new approach for biological system characterization is explored and the significance of this work are listed as follows:

a) Experimental work has been carried out to show the feasibility of the proposed system to detect fluid flow change and determine the phase difference under different induced pressure voltage.

b) The biological tissues characterization was carried out using the measured PA signal under different experimental condition. The results showed an overall sensitivity of 77.3 % using the assembled system in distinguishing different tissues sample.

c) The developed PA system has been clinically tested on human subjects to retrieve the blood perfusion information.

1.7 Outline of thesis

The organization of the thesis is as follows:

Chapter 2 reviewed the articles and existing system that is related to the study. Comparisons between the system specifications and limitations are made.

Chapter 3 described how the system worked from the development stage until the application stages.

Chapter 4 demonstrates the result and analysis of this project. This chapter presented the results obtained using the constructed system.

Chapter 5 presented the conclusion and recommendation of this project. There are also discussions on future works that can be done for future applications of this system.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

In this chapter, the previous works are discussed, this chapter also reviews the background and previous projects involving photoacoustic imaging. It covers the related technical and theoretical knowledge required for the completion of this project.

This chapter begins with brief discussion on current imaging techniques in section 2.2 followed by an overview of PA imaging and its characteristics in section 2.3 which discussed on fundamental factors that affect the PA imaging. The description and study of four main types of PA imaging are presents in section 2.4, which include different types of photoacoustic modalities. Timeline evolution of PA imaging is shown in sub-section 2.4.5 and section 2.5 describes on comparison of PA imaging modalities. The current technology using PA imaging in medical field is discussed in section 2.6. A review of previous works involving PA imaging on fluid flow visualization and biological tissues characterization are stated in section 2.7. This is followed by section 2.8, which explains on factors affecting the changes of phase values of tissues. Section 2.9 in this chapter discusses on the commonly used image reconstruction technique involving acoustic signals.

REFERENCES

[1] S. M. Erturk, C. Johnston, C. Tempany-Afdhal, and A. D. Van den Abbeele, "Imaging Tools in Human Research," in *Clinical and Translational Science*, ed: Elsevier, pp. 87-104, 2009.

[2] A. G. Bell, "ART. XXXIV.--On the Production and Reproduction of Sound by Light," *American Journal of Science (1880-1910)*, vol. 20, pp. 305, 1880.

[3] A. A. Oraevsky, E. V. Savateeva, S. V. Solomatin, A. A. Karabutov, V. G. Andreev, Z. Gatalica, *et al.*, "Optoacoustic imaging of blood for visualization and diagnostics of breast cancer," in *Biomedical Optoacoustics III*, pp. 81-95, 2002.

[4] X. Chen, "Nanoplatform-based molecular imaging," John Wiley & Sons, 2011.

[5] J. Shah, S. Park, S. R. Aglyamov, T. Larson, L. Ma, K. V. Sokolov, *et al.*, "Photoacoustic imaging and temperature measurement for photothermal cancer therapy," *Journal of biomedical optics*, vol. 13, pp. 034024, 2008.

[6] R. Li, P. Wang, L. Lan, F. P. Lloyd, C. J. Goergen, S. Chen, *et al.*, "Assessing breast tumor margin by multispectral photoacoustic tomography," *Biomedical optics express*, vol. 6, pp. 1273-1281, 2015.

[7] H. Ke, C. Liu, L. V. Wang, T. N. Erpelding, and L. Jankovic, "Performance characterization of an integrated ultrasound, photoacoustic, and thermoacoustic imaging system," *Journal of biomedical optics*, vol. 17, pp. 056010, 2012.

[8] A. Chopra, L. Shan, W. Eckelman, K. Leung, M. Latterner, S. H. Bryant, *et al.*, "Molecular imaging and contrast agent database (MICAD): evolution and progress," *Molecular Imaging and Biology*, vol. 14, pp. 4-13, 2012.

[9] A. de la Zerda, "Photoacoustic Molecular Imaging and its Biophysical Applications," *Biophysical Journal*, vol. 104, pp. 185a, 2013.

[10] J. Xia, J. Yao, and L. V. Wang, "Photoacoustic tomography: principles and advances," *Electromagnetic waves (Cambridge, Mass.)*, vol. 147, pp. 1, 2014.

[11] J. Laufer, D. Delpy, C. Elwell, and P. Beard, "Quantitative spatially resolved measurement of tissue chromophore concentrations using photoacoustic spectroscopy: application to the measurement of blood oxygenation and haemoglobin concentration," *Physics in Medicine & Biology*, vol. 52, pp. 141, 2006.

[12] J. L. Su, A. B. Karpiouk, B. Wang, and S. Y. Emelianov, "Photoacoustic imaging of clinical metal needles in tissue," *Journal of biomedical optics*, vol. 15, pp. 021309, 2010.

[13] S. Mallidi, G. P. Luke, and S. Emelianov, "Photoacoustic imaging in cancer detection, diagnosis, and treatment guidance," *Trends in biotechnology*, vol. 29, pp. 213-221, 2011.

[14] B. Wang, J. L. Su, J. Amirian, S. H. Litovsky, R. Smalling, and S. Emelianov, "Detection of lipid in atherosclerotic vessels using ultrasound-guided spectroscopic intravascular photoacoustic imaging," *Optics express*, vol. 18, pp. 4889-4897, 2010.

[15] P. Beard, "Biomedical photoacoustic imaging," *Interface focus*, vol. 1, pp. 602-631, 2011.

[16] Kementerian Kesihatan Malaysia, "Eleventh Malaysia Plan 2016-2020, Anchoring growth on people-Kementerian Kesihatan Malaysia," Percetakan Nasional Malaysia Berhad, 21 May 2015.

[17] M. A. W. Yusof and H. M. Ali, "Radiological emergency: Malaysian preparedness and response," *Radiation protection dosimetry*, vol. 146, pp. 38-41, 2011.

[18] National Kidney Foundation, "Contrast Dye and the kidneys," A to Z Health Guide, New York 10016, 2019.

[19] C. P. Yu, D. K. Whynes, and T. H. Sach, "Equity in health care financing: The case of Malaysia," *International journal for equity in health*, vol. 7, pp. 15, 2008.

[20] E. J. Keliher, Y. X. Ye, G. R. Wojtkiewicz, A. D. Aguirre, B. Tricot, M. L. Senders, *et al.*, "Polyglucose nanoparticles with renal elimination and macrophage avidity facilitate PET imaging in ischaemic heart disease," *Nature communications*, vol. 8, pp. 1-12, 2017.

[21] A. M. Muehe, D. Feng, R. von Eyben, S. Luna-Fineman, M. P. Link, T. Muthig, *et al.*, "Safety report of ferumoxytol for magnetic resonance imaging in children and young adults," *Investigative radiology,* vol. 51, pp. 221, 2016.

[22] K. Khoo, H. Tan, Y. Liew, J. Deslypere, and E. Janus, "Lipids and coronary heart disease in Asia," *Atherosclerosis,* vol. 169, pp. 1-10, 2003.

[23] G. C. C. Lim, "Overview of cancer in Malaysia," *Japanese Journal of Clinical Oncology,* vol. 32, pp. S37-S42, 2002.

[24] E. Sauer, A. Extra, P. Cachee, and C. Courts, "Identification of organ tissue types and skin from forensic samples by microRNA expression analysis," *Forensic Science International: Genetics,* vol. 28, pp. 99-110, 2017.

[25] E. W. Esch, A. Bahinski, and D. Huh, "Organs-on-chips at the frontiers of drug discovery," *Nature reviews Drug discovery,* vol. 14, pp. 248, 2015.

[26] A. N. Singh, P. K. Sharma, and Y. Agrawal, "Multifarious applications of photoacoustic spectrophotometer and its importance in forensic investigation," *Applied Spectroscopy Reviews,* vol. 49, pp. 618-634, 2014.

[27] D. A. Boas, S. Sakadzic, J. J. Selb, P. Farzam, M. A. Franceschini, and S. A. Carp, "Establishing the diffuse correlation spectroscopy signal relationship with blood flow," *Neurophotonics,* vol. 3, pp. 031412, 2016.

[28] D. Katanov, G. Gompper, and D. A. Fedosov, "Microvascular blood flow resistance: role of red blood cell migration and dispersion," *Microvascular research,* vol. 99, pp. 57-66, 2015.

[29] K. K. Shung, *Diagnostic ultrasound: Imaging and blood flow measurements*: CRC press, 2015.

[30] P. A. Magnin, E. I. McNamara, R. W. Bowden, and R. J. Solomon, "Apparatus and methods for low-cost intravascular ultrasound imaging and for crossing severe vascular occlusions," *Volcano Corporation (San Diego, CA, US),* vol. 13/935050, 25 October 2016.

[31] B. A. Cox, K. M. Kelly, P. Ko, L. Hertzog, and S. C. Stain, "Ultrasound characteristics of breast carcinoma," *The American Surgeon,* vol. 64, pp. 934, 1998.

[32] H. Yang, W. Cai, L. Xu, X. Lv, Y. Qiao, P. Li, *et al.*, "Nanobubble–Affibody: Novel ultrasound contrast agents for targeted molecular ultrasound imaging of tumor," *Biomaterials,* vol. 37, pp. 279-288, 2015.

[33] M. A. Brown, R. C. Semelka, and B. M. Dale, "MRI: basic principles and applications," *John Wiley & Sons*, 2015.

[34] M. D. Schnall, "Breast imaging technology Application of magnetic resonance imaging to early detection of breast cancer," *Breast Cancer Research*, vol. 3, pp. 17, 2000.

[35] A. Sombke, E. Lipke, P. Michalik, G. Uhl, and S. Harzsch, "Potential and limitations of X-Ray micro-computed tomography in arthropod neuroanatomy: A methodological and comparative survey," *Journal of Comparative Neurology*, vol. 523, pp. 1281-1295, 2015.

[36] M. Y. Berezin, "Nanotechnology for biomedical imaging and diagnostics: from nanoparticle design to clinical applications," *Wiley Online Library*, 2015.

[37] K. M. Kelly, B. Choi, S. McFarlane, A. Motosue, B. Jung, M. H. Khan, *et al.*, "Description and analysis of treatments for port-wine stain birthmarks," *Archives of facial plastic surgery*, vol. 7, pp. 287-294, 2005.

[38] E. Ruggiero, S. Alonso-de Castro, A. Habtemariam, and L. Salassa, "Upconverting nanoparticles for the near infrared photoactivation of transition metal complexes: new opportunities and challenges in medicinal inorganic photochemistry," *Dalton Transactions*, vol. 45, pp. 13012-13020, 2016.

[39] K. Irisawa, T. Hirasawa, K. Hirota, K. Tsujita, and M. Ishihara, "Influence of laser pulse width to the photoacoustic temporal waveform and the image resolution with a solid-state excitation laser," in *Photons Plus Ultrasound: Imaging and Sensing 2012*, pp. 82232W, 2012.

[40] R. H. Silverman, E. Vinarsky, and D. J. Coleman, "The Effect of Transducer Bandwidth on Ultrasonic," *Retina*, vol. 15, pp. 37-42, 1995.

[41] A. Taylor, S. Branch, H. Crews, and D. Halls, "Photoacoustic Spectroscopy, Applications," *Chemistry*, vol. 62, pp. 84R, 1999.

[42] M. Viegerov, "Eine Methode der Gasanalyse, Beruhend auf der Optisch-Akustischen Tyndall-R öntgenerscheinung," in *Dokl. Akad. Nauk SSSR*, pp. 687-688, 1938.

[43] D. R. Siebert, G. A. West, and J. J. Barrett, "Gaseous trace analysis using pulsed photoacoustic Raman spectroscopy," *Applied optics*, vol. 19, pp. 53-60, 1980.

[44] T. Schmid, "Photoacoustic spectroscopy for process analysis," *Analytical and bioanalytical chemistry*, vol. 384, pp. 1071-1086, 2006.

[45] S. S. Choi, A. Mandelis, X. Guo, B. Lashkari, S. Kellnberger, and V. Ntziachristos, "Wavelength-Modulated Differential Photoacoustic Spectroscopy (WM-DPAS) for noninvasive early cancer detection and tissue hypoxia monitoring," *Journal of biophotonics,* vol. 9, pp. 388-395, 2016.

[46] J. McClelland, "Photoacoustic spectroscopy," *Analytical Chemistry,* vol. 55, pp. 89-105, 1983.

[47] T. H. Bok, E. Hysi, and M. C. Kolios, "In vitro photoacoustic spectroscopy of pulsatile blood flow: Probing the interrelationship between red blood cell aggregation and oxygen saturation," *Journal of biophotonics,* pp. e201700300, 2018.

[48] T.J. Yoon and Y.-S. Cho, "Recent advances in photoacoustic endoscopy," *World journal of gastrointestinal endoscopy,* vol. 5, pp. 534, 2013.

[49] N. Beziere and V. Ntziachristos, "Optoacoustic imaging: an emerging modality for the gastrointestinal tract," *Gastroenterology,* vol. 141, pp. 1979-1985, 2011.

[50] J. A. Viator, G. Au, G. Paltauf, S. L. Jacques, S. A. Prahl, H. Ren, *et al.*, "Clinical testing of a photoacoustic probe for port wine stain depth determination," *Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery,* vol. 30, pp. 141-148, 2002.

[51] J. M. Yang, K. Maslov, H.-C. Yang, Q. Zhou, K. K. Shung, and L. V. Wang, "Photoacoustic endoscopy," *Optics letters,* vol. 34, pp. 1591-1593, 2009.

[52] J. M. Yang, C. Favazza, R. Chen, K. Maslov, X. Cai, Q. Zhou, *et al.*, "Volumetric photoacoustic endoscopy of upper gastrointestinal tract: ultrasonic transducer technology development," in *Photons Plus Ultrasound: Imaging and Sensing 2011*, pp. 78990D, 2011.

[53] X. Ji, K. Xiong, S. Yang, and D. Xing, "Intravascular confocal photoacoustic endoscope with dual-element ultrasonic transducer," *Optics Express,* vol. 23, pp. 9130-9136, 2015.

[54] N. Q. Bui, K. K. Hlaing, V. P. Nguyen, T. H. Nguyen, Y. O. Oh, X. F. Fan, *et al.*, "Intravascular ultrasonic–photoacoustic (IVUP) endoscope with 2.2-mm diameter catheter for medical imaging," *Computerized Medical Imaging and Graphics,* vol. 45, pp. 57-62, 2015.

[55] S. Tang, J. Chen, P. Samant, K. Stratton, and L. Xiang, "Transurethral photoacoustic endoscopy for prostate cancer: a simulation study," *IEEE transactions on medical imaging,* vol. 35, pp. 1780-1787, 2016.

[56] E. M. Strohm, M. J. Moore, and M. C. Kolios, "Single cell photoacoustic microscopy: a review," *IEEE Journal of Selected Topics in Quantum Electronics*, vol. 22, pp. 137-151, 2016.

[57] A. Hariri, A. Fatima, N. Mohammadian, N. Bely, and M. Nasiriavanaki, "Towards low cost photoacoustic microscopy system for evaluation of skin health," in *Imaging Spectrometry XXI*, pp. 99760X, 2016.

[58] B. Ning, N. Sun, R. Cao, R. Chen, K. K. Shung, J. A. Hossack, *et al.*, "Ultrasound-aided multi-parametric photoacoustic microscopy of the mouse brain," *Scientific reports*, vol. 5, pp. 18775, 2015.

[59] L. Lin, P. Zhang, S. Xu, J. Shi, L. Li, J. Yao, *et al.*, "Handheld optical-resolution photoacoustic microscopy," *Journal of biomedical optics*, vol. 22, pp. 041002, 2016.

[60] M. Martinho Costa, A. Shah, I. Rivens, C. Box, T. O'Shea, E. Papaevangelou, *et al.*, "Quantitative photoacoustic imaging study of tumours in vivo: Baseline variations in quantitative measurements," 2019.

[61] J. Yao and L. V. Wang, "Photoacoustic tomography: fundamentals, advances and prospects," *Contrast media & molecular imaging*, vol. 6, pp. 332-345, 2011.

[62] S. E. Bohndiek, L. S. Sasportas, S. Machtaler, J. V. Jokerst, S. Hori, and S. S. Gambhir, "Photoacoustic tomography detects early vessel regression and normalization during ovarian tumor response to the antiangiogenic therapy trebananib," *Journal of nuclear medicine: official publication, Society of Nuclear Medicine*, vol. 56, pp. 1942, 2015.

[63] J. Yao and L. V. Wang, "Breakthroughs in photonics 2013: photoacoustic tomography in biomedicine," *IEEE photonics journal*, vol. 6, pp. 1-6, 2014.

[64] J. Yao, J. Xia, and L. V. Wang, "Multiscale functional and molecular photoacoustic tomography," *Ultrasonic imaging*, vol. 38, pp. 44-62, 2016.

[65] P. K. Upputuri and M. Pramanik, "Performance characterization of low-cost, high-speed, portable pulsed laser diode photoacoustic tomography (PLD-PAT) system," *Biomedical optics express*, vol. 6, pp. 4118-4129, 2015.

[66] X. Wang, Y. Pang, G. Ku, X. Xie, G. Stoica, and L. V. Wang, "Noninvasive laser-induced photoacoustic tomography for structural and functional in vivo imaging of the brain," *Nature biotechnology*, vol. 21, pp. 803, 2003.

[67] L. V. Wang and S. Hu, "Photoacoustic tomography: in vivo imaging from organelles to organs," *science,* vol. 335, pp. 1458-1462, 2012.

[68] P. Burgholzer, H. Grün, and A. Sonnleitner, "Photoacoustic tomography: Sounding out fluorescent proteins," *Nature Photonics,* vol. 3, pp. 378, 2009.

[69] L. Xiang, B. Wang, L. Ji, and H. Jiang, "4-D photoacoustic tomography," *Scientific reports,* vol. 3, pp. 1113, 2013.

[70] M. Heijblom, D. Piras, F. M. van den Engh, J. M. Klaase, M. Brinkhuis, W. Steenbergen, *et al.*, "Photoacoustic imaging of breast tumor vascularization: a comparison with MRI and histopathology," in *European Conference on Biomedical Optics*, pp. 880004, 2013.

[71] D. A. Nedosekin, M. Sarimollaoglu, E. V. Shashkov, E. I. Galanzha, and V. P. Zharov, "Ultra-fast photoacoustic flow cytometry with a 0.5 MHz pulse repetition rate nanosecond laser," *Optics express,* vol. 18, pp. 8605-8620, 2010.

[72] W. Li, L. Xing, L. Tao, Z. Qian, and L. Nie, "In vivo monitoring of blood-brain barrier leakage by using photoacoustic microscopy," in *2014 IEEE Biomedical Circuits and Systems Conference (BioCAS) Proceedings*, pp. 93-96, 2014.

[73] T. J. Allen and P. C. Beard, "High power visible light emitting diodes as pulsed excitation sources for biomedical photoacoustics," *Biomedical optics express,* vol. 7, pp. 1260-1270, 2016.

[74] J. Lavaud, M. Henry, J. L. Coll, and V. Josserand, "Exploration of melanoma metastases in mice brains using endogenous contrast photoacoustic imaging," *International journal of pharmaceutics,* vol. 532, pp. 704-709, 2017.

[75] A. Garcia-Uribe, T. N. Erpelding, A. Krumholz, H. Ke, K. Maslov, C. Appleton, *et al.*, "Dual-modality photoacoustic and ultrasound imaging system for noninvasive sentinel lymph node detection in patients with breast cancer," *Scientific reports,* vol. 5, pp. 15748, 2015.

[76] S. Tan, H. Teh, J. K. Mancer, and W. Poh, "Improving B mode ultrasound evaluation of breast lesions with real-time ultrasound elastography—a clinical approach," *The Breast,* vol. 17, pp. 252-257, 2008.

[77] H. Haj-Hassan, A. Chaddad, Y. Harkouss, C. Desrosiers, M. Toews, and C. Tanougast, "Classifications of multispectral colorectal cancer tissues using convolution neural network," *Journal of pathology informatics,* vol. 8, 2017.

[78] J. L. Rose, "Ultrasonic guided waves in solid media," *Cambridge university press*, 2014.

[79] A. Cassone, "Method for treating circulatory disorders with acoustic waves," *Cassone Alphonse*, vol. 601/47, 31 December 2002.

[80] L. H. Hudgins and P. A. Chandraratna, "Non-invasive acoustic screening device for coronary stenosis," *Integrated Medical Systems*, vol. 09/164618, 11 April 2000.

[81] C. Vlachopoulos, M. O'Rourke, and W. W. Nichols, "McDonald's blood flow in arteries: theoretical, experimental and clinical principles," *CRC press*, 2011.

[82] T. Somer and H. J. Meiselman, "Disorders of blood viscosity," *Annals of medicine*, vol. 25, pp. 31-39, 1993.

[83] M. S. Olufsen, J. T. Ottesen, H. T. Tran, L. M. Ellwein, L. A. Lipsitz, and V. Novak, "Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation," *Journal of Applied Physiology*, vol. 99, pp. 1523-1537, 2005.

[84] G. M. London and A. P. Guerin, "Influence of arterial pulse and reflected waves on blood pressure and cardiac function," *American heart journal*, vol. 138, pp. S220-S224, 1999.

[85] E. O. Ofili, M. J. Kern, J. A. S. Vrain, T. J. Donohue, R. Bach, B. Al-Joundi, *et al.*, "Differential characterization of blood flow, velocity, and vascular resistance between proximal and distal normal epicardial human coronary arteries: analysis by intracoronary Doppler spectral flow velocity," *American heart journal*, vol. 130, pp. 37-46, 1995.

[86] Y. Sun and N. Thakor, "Photoplethysmography revisited: from contact to noncontact, from point to imaging," *IEEE Transactions on Biomedical Engineering*, vol. 63, pp. 463-477, 2015.

[87] C. E. Riva, M. Geiser, B. L. Petrig, and O. B. F. R. Association, "Ocular blood flow assessment using continuous laser Doppler flowmetry," *Acta ophthalmologica*, vol. 88, pp. 622-629, 2010.

[88] T. H. Bok, E. Hysi, M. N. Fadhel, and M. C. Kolios, "Simulation of Photoacoustic Imaging of Red Blood Cell Aggregation Using a Numerical Model of Pulsatile Blood Flow," in *2018 IEEE International Ultrasonics Symposium (IUS)*, pp. 1-4, 2018.

[89] S. Ueda, I. Kuji, T. Shigekawa, H. Takeuchi, H. Sano, E. Hirokawa, *et al.*, "Optical imaging for monitoring tumor oxygenation response after initiation of

single-agent bevacizumab followed by cytotoxic chemotherapy in breast cancer patients," *PLoS One,* vol. 9, pp. e98715, 2014.

[90] S. H. Chung, R. Mehta, B. J. Tromberg, and A. G. Yodh, "Non-invasive measurement of deep tissue temperature changes caused by apoptosis during breast cancer neoadjuvant chemotherapy: a case study," *Journal of innovative optical health sciences,* vol. 4, pp. 361-372, 2011.

[91] P. Vaupel, S. Briest, and M. Hockel, "Hypoxia in breast cancer: pathogenesis, characterization and biological/therapeutic implications," *Wiener Medizinische Wochenschrift,* vol. 152, pp. 334-342, 2002.

[92] W. Liu and H. F. Zhang, "Photoacoustic imaging of the eye: a mini review," *Photoacoustics,* vol. 4, pp. 112-123, 2016.

[93] C. Sun, L. Wen, J. Zeng, Y. Wang, Q. Sun, L. Deng, *et al.*, "One-pot solventless preparation of Pegylated black phosphorus nanoparticles for photoacoustic imaging and photothermal therapy of cancer," *Biomaterials,* vol. 91, pp. 81-89, 2016.

[94] W. Li and X. Chen, "Gold nanoparticles for photoacoustic imaging," *Nanomedicine,* vol. 10, pp. 299-320, 2015.

[95] J. Märk, F.-J. Schmitt, C. Theiss, H. Dortay, T. Friedrich, and J. Laufer, "Photoacoustic imaging of fluorophores using pump-probe excitation," *Biomedical optics express,* vol. 6, pp. 2522-2535, 2015.

[96] F. Gao, R. Zhang, X. Feng, S. Liu, R. Ding, R. Kishor, *et al.*, "Phase-domain photoacoustic sensing," *Applied Physics Letters,* vol. 110, pp. 033701, 2017.

[97] B. Zhao, Y. Wang, C. Gao, T. Liu, and Q. Sun, "Thermal properties of porcine tissues determined by modified photoacoustic piezoelectric technique," *International Journal of Thermophysics,* vol. 34, pp. 1513-1518, 2013.

[98] B. Lashkari, E. Dovlo, S. Dhody, and A. Mandelis, "Frequency-domain photoacoustic phase spectroscopy: A fluence-independent approach for quantitative probing of hemoglobin oxygen saturation," *IEEE Journal of Selected Topics in Quantum Electronics,* vol. 22, pp. 127-136, 2015.

[99] I. Juvells, S. Vallmitjana, A. Carnicer, and J. Campos, "The role of amplitude and phase of the Fourier transform in the digital image processing," *American Journal of Physics,* vol. 59, pp. 744-748, 1991.

[100] R. R. Diehl, D. Linden, D. Lucke, and P. Berlit, "Phase relationship between cerebral blood flow velocity and blood pressure: a clinical test of autoregulation," *Stroke,* vol. 26, pp. 1801-1804, 1995.

[101] D. C. Giancoli, "Physics: Principles with applications," *Boston: Pearson,* 2016.

[102] Y. Pu, J. Chen, W. Wang, and R. R. Alfano, "Basic Optical Scattering Parameter of the Brain and Prostate Tissues in the Spectral Range of 400–2400 nm," in *Neurophotonics and Biomedical Spectroscopy*, ed: Elsevier, pp. 229-252, 2019.

[103] H. K. Hughes, "Beer's law and the optimum transmittance in absorption measurements," *Applied optics,* vol. 2, pp. 937-945, 1963.

[104] J. P. Farkas, J. E. Hoopman, and J. M. Kenkel, "Five parameters you must understand to master control of your laser/light-based devices," *Aesthetic surgery journal,* pp. 1059-1064, 2013.

[105] T. Ma, X. Zhang, C. T. Chiu, R. Chen, K. K. Shung, Q. Zhou, *et al.*, "Systematic study of high-frequency ultrasonic transducer design for laser-scanning photoacoustic ophthalmoscopy," *Journal of biomedical optics,* vol. 19, pp. 016015, 2014.

[106] W. McDicken and T. Anderson, "Basic physics of medical ultrasound," *Blood,* vol. 1570, pp. 105, 2011.

[107] R. J. van den Bijgaart, D. C. Eikelenboom, M. Hoogenboom, J. J. Fütterer, M. H. den Brok, and G. J. Adema, "Thermal and mechanical high-intensity focused ultrasound: perspectives on tumor ablation, immune effects and combination strategies," *Cancer Immunology, Immunotherapy,* vol. 66, pp. 247-258, 2017.

[108] M. K. Karmakar and W. H. Kwok, "Ultrasound-guided regional anesthesia," in *A Practice of Anesthesia for Infants and Children*, ed: Elsevier, pp. 988-1022. e4, 2019.

[109] I. C. G. S. Consortium, "Sequence and comparative analysis of the chicken genome provide unique perspectives on vertebrate evolution," *Nature,* vol. 432, pp. 695, 2004.

[110] A. A. Oraevsky, V. A. Andreev, A. A. Karabutov, and R. O. Esenaliev, "Two-dimensional optoacoustic tomography: transducer array and image reconstruction algorithm," in *Laser-Tissue Interaction X: Photochemical, Photothermal, and Photomechanical*, pp. 256-267, 1999.

[111] M. Mozaffarzadeh, A. Mahloojifar, and M. Orooji, "Image enhancement and noise reduction using modified delay-multiply-and-sum beamformer: Application to medical photoacoustic imaging," in *2017 Iranian Conference on Electrical Engineering (ICEE)*, pp. 65-69, 2017.

[112] S. K. Kalva and M. Pramanik, "Experimental validation of tangential resolution improvement in photoacoustic tomography using modified delay-and-sum reconstruction algorithm," *Journal of Biomedical Optics*, vol. 21, pp. 086011, 2016.

[113] A. P. Jathoul, J. Laufer, O. Ogunlade, B. Treeby, B. Cox, E. Zhang, *et al.*, "Deep in vivo photoacoustic imaging of mammalian tissues using a tyrosinase-based genetic reporter," *Nature Photonics*, vol. 9, pp. 239, 2015.

[114] B. Cox and P. C. Beard, "Modeling photoacoustic propagation in tissue using k-space techniques," in *Photoacoustic Imaging and Spectroscopy*, ed: *CRC Press*, pp. 25-34, 2017.

[115] T. K. Jhamb, V. Rejathalal, and V. Govindan, "A review on image reconstruction through mri k-space data," *International Journal of Image, Graphics and Signal Processing*, vol. 7, pp. 42, 2015.

[116] D. Krol, A. Lorenc, and R. Swiceinski, "Detecting laterality and nasality in speech with the use of a multi-channel recorder," in *2015 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, pp. 5147-5151, 2015.

[117] C. B. Paschal and H. D. Morris, "K-space in the clinic," *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, vol. 19, pp. 145-159, 2004.

[118] M. Akay, "Wiley encyclopedia of biomedical engineering," *Wiley-Interscience*, 2006.

[119] K. Zhou, Z. Zhang, and S. Yang, "Photoacoustic image reconstruction," 2013.

[120] H. Hassanisaber, L. Rouleau, and N. Faucheux, "Cell-Biomaterial Biohybrid Systems," *Frontiers in Bioscience (Landmark edition) Europe PMC*, vol. 24:994-1023, 1 March 2019.

[121] R. Konrad, N. Padmanaban, K. Molner, E. A. Cooper, and G. Wetzstein, "Accommodation-invariant computational near-eye displays," *ACM Transactions on Graphics (TOG)*, vol. 36, pp. 88, 2017.

[122] C. M. Langton and C. F. Njeh, "The physical measurement of bone," *CRC Press*, 2016.

[123] A. Scorza, S. Conforto, C. d'Anna, and S. Sciuto, "A comparative study on the influence of probe placement on quality assurance measurements in B-mode Ultrasound by means of ultrasound phantoms," *The open biomedical engineering journal*, vol. 9, pp. 164, 2015.

[124] T. Azuma, S. I. Umemura, and Y. Miwa, "Ultrasonic imaging system and method," *Acoustical Society of America Journal*, vol. 125, issue 6, pp. 4109, 2009.

[125] I. C. Christov, V. Cognet, T. C. Shidhore, and H. A. Stone, "Flow rate–pressure drop relation for deformable shallow microfluidic channels," *Journal of Fluid Mechanics*, vol. 841, pp. 267-286, 2018.

[126] N. Raine-Fenning, N. Nordin, K. Ramnarine, B. Campbell, J. Clewes, A. Perkins, *et al.*, "Determining the relationship between three-dimensional power Doppler data and true blood flow characteristics: an in-vitro flow phantom experiment," *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, vol. 32, pp. 540-550, 2008.

[127] C. B. Gurung, "Practical Guides to Testing and Commissioning of Mechanical, Electrical and Plumbing (Mep) Installations," *Partridge Publishing Singapore*, 2019.

[128] Z. W. Geem, "Harmony search in water pump switching problem," in *International Conference on Natural Computation*, pp. 751-760, 2005.

[129] D. L. Franklin, W. Schlegel, and R. F. Rushmer, "Blood flow measured by Doppler frequency shift of back-scattered ultrasound," *Science*, vol. 134, pp. 564-565, 1961.

[130] A. A. Oglat, M. Matjafri, N. Suardi, M. A. Oqlat, M. A. Abdelrahman, and A. A. Oqlat, "A review of medical doppler ultrasonography of blood flow in general and especially in common carotid artery," *Journal of medical ultrasound*, vol. 26, pp. 3, 2018.

[131] P. Tortoli, M. Lenge, D. Righi, G. Ciuti, H. Liebgott, and S. Ricci, "Comparison of carotid artery blood velocity measurements by vector and standard Doppler approaches," *Ultrasound in medicine & biology*, vol. 41, pp. 1354-1362, 2015.

[132] J. Markowitz, "Probe selection, machine controls and equipment," *Carmody KA, Moore CL, Feller-Copman D. Handbook of critical care and emergency ultrasound. USA: McGraw-Hill Medical,* pp. 25-38, 2011.

[133] O. T. Von Ramm and S. W. Smith, "Beam steering with linear arrays," *IEEE transactions on biomedical engineering,* pp. 438-452, 1983.

[134] J. Keshvari, R. Keshvari, and S. Lang, "The effect of increase in dielectric values on specific absorption rate (SAR) in eye and head tissues following 900, 1800 and 2450 MHz radio frequency (RF) exposure," *Physics in Medicine & Biology,* vol. 51, pp. 1463, 2006.

[135] S. R. Smith and K. R. Foster, "Dielectric properties of low-water-content tissues," *Physics in Medicine & Biology,* vol. 30, pp. 965, 1985.

[136] L. Gun, D. Ning, and Z. Liang, "Effective permittivity of biological tissue: comparison of theoretical model and experiment," *Mathematical Problems in Engineering,* vol. 2017, 2017.

[137] L. V. Wang, X. Zhao, H. Sun, and G. Ku, "Microwave-induced acoustic imaging of biological tissues," *Review of scientific instruments,* vol. 70, pp. 3744-3748, 1999.

[138] A. M. Zysk, S. G. Adie, J. J. Armstrong, M. S. Leigh, A. Paduch, D. D. Sampson, *et al.*, "Needle-based refractive index measurement using low-coherence interferometry," *Optics letters,* vol. 32, pp. 385-387, 2007.

[139] N. Piri, A. Shams-Nateri, and J. Mokhtari, "The relationship between refractive index and optical properties of absorbing nanoparticle," *Color Research & Application,* vol. 41, pp. 477-483, 2016.

[140] Y. Merkulov and I. Markov, "Ultrasound diagnostic for sturgeon: Practical guideline: 2th edition," *Applied Sturgeon Agency,* ISBN 978-5-6042433-1-2, 2019.

[141] S. E. Shelton, Y. Z. Lee, M. Lee, E. Cherin, F. S. Foster, S. R. Aylward, *et al.*, "Quantification of microvascular tortuosity during tumor evolution using acoustic angiography," *Ultrasound in medicine & biology,* vol. 41, pp. 1896-1904, 2015.

[142] K. Qian, C. Wu, F. Xiao, Y. Zheng, Y. Zhang, Z. Yang, *et al.*, "Acousticcardiogram: Monitoring heartbeats using acoustic signals on smart devices," in *IEEE INFOCOM 2018-IEEE Conference on Computer Communications*, pp. 1574-1582, 2018.

[143] R. Abbasi-Kesbi, A. Valipour, and K. Imani, "Cardiorespiratory system monitoring using a developed acoustic sensor," *Healthcare technology letters*, vol. 5, pp. 7-12, 2018.

[144] A. R. Pries, T. W. Secomb, H. Jacobs, M. Sperandio, K. Osterloh, and P. Gaehtgens, "Microvascular blood flow resistance: role of endothelial surface layer," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 273, pp. H2272-H2279, 1997.

[145] N. Charkoudian, "Skin blood flow in adult human thermoregulation: how it works, when it does not, and why," in *Mayo clinic proceedings*, pp. 603-612, 2003.